IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	B. Zikria
Serial No.:	08/837840
Filed:	April 22, 1997
For:	Capillary Membrane Stabilization and Reduction Of Tissue Injury Through IV Biodegradable Macromolecules With Antioxidants . . .
Group Art Unit:	1023
Examiner:	Gary Kunz

Assistant Commissioner for Patents
Washington, D.C. 20231 April 1, 1999

BRIEF OF APPELLANTS

This is an appeal from the final rejection of the Examiner dated November 24, 1998, rejecting claims 1-20 all of the claims pending in the application.

The brief is accompanied by the requisite fee.

REAL PARTY IN INTEREST

The inventor Bashir Zikria is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS (37 C.F.R. 1.92(c)(1))

The application was filed with twenty (20) claims of which three (3) were independent (claims 1, 19 and 20).

All of the claims were rejected on May 11, 1998.

In applicant's response filed September 11, 1998, claims 1 and 20 were amended.

The examiner's next office action (November 24, 1998) was a final rejection of all of the claims (claims 1-20).

The status of the claims as set out in paper no.6 was as follows:

allowed claims - - none

claims objected to - - none

claims rejected - - 1-20

STATUS OF AMENDMENTS (37 C.F.R. 1.192 (c)(2))

The claims as set out in the Appendix include the entered amendments.

SUMMARY OF THE INVENTION

The method as herein claimed is directed to treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions during a period of increased capillary permeability and for preventing the harmful effects of free radicals on cellular membranes and other organelles. The method comprises (claim 1) administering to a subject an effective amount of composition comprising at least one polysaccharide selected from hydroxyethyl starch and dextran of varying molecular sizes and at least one of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C. The composition of the invention is the formulation comprising hydroxyethyl starch and/or dextran and at least one antioxidant as above set forth in admixture with a pharmaceutically

acceptable carrier.

The compositions contain the polysaccharide macromolecules in a molecular size and concentration to effectively stabilize the capillary membrane. The stabilization effect is accomplished by a biophysical/biochemical process due to the adhesiveness and configuration of the macro molecules and because of their size. The treatment is benign as the macromolecules and antioxidants are non-toxic and biodegradable. The uncontrolled activity of free radicals (superoxide, singlet oxygen and the hydroxyls) results in damage to cells, tissues and organs. Studies of free radical pathology has given us a better understanding of degenerative diseases, cancer and the aging process. Free radical pathology plays a part in immune system suppression and susceptibility to infectious diseases. It is the extreme excitability of free radicals that makes them dangerous. They can destroy cell membranes causing cell fluid leakage and at the same time prevent the intake of cell nutrients. Free radicals also interact with DNA and RNA causing the production of mutations and may also cause uncontrolled fusion of large cell molecules (cross linking). The latter process is responsible for hardening of artery walls a factor in atherosclerosis and hypertension as well as affecting the aging process.

Admittedly, free radical activity under the proper control of the body serves many useful and essential functions. For example, the immune system can use potentially dangerous free radicals liberated by polymorphonuclear cells during inflammation. Similarly, without controlled free radical reactions there would be no synthesis of prostaglandins that regulate many of our physiological functions.

Given the threat to the integrity of cells from uncontrolled activity of highly reactive

species of free radicals it is important that antioxidants be available to neutralize them.

The protective effects of the antioxidants are attributable to their activity in neutralizing the harmful effects of free radicals and are in the case of the invention provided by including at least one of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl, rutoside cyclic adenosine monophosphate and Vitamin C.

The compositions of the invention are prepared using the conventional carriers as for example 0.9% saline, 5% dextrose or Ringer's lactate and administered by intravenous injection.

ISSUES (37 C.F.R. 1.192(c)(4))

The Examiner has rejected claims 1-20 under 35 U.S.C. 103 as being unpatentable over Zikria in view of Weiss, Munkes, *et al.*, and Gerdin.

It is the Examiner's position that Zikria teaches the use of hydroxyethyl starch and hydroxyethyl dextran as a means for treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions. The Examiner concedes that Zikria does not teach the use of antioxidants along with the hydroxyethyl starch or dextran.

Weiss (superoxide dismutase), Munkes (cAMP) and Gerdin (hydroxyethyl rutoside) are relied as supplying this omission. Specifically the Examiner states that it would have been obvious to modify Zikria "by adding any art recognized antioxidant molecule such as Vitamin C, superoxide dismutase, catalase glutathione peroxidase, hydroxyethyl rutoside or cAMP (as suggested by Weiss, Munkres and Gerdin) for the expressed purpose of protecting capillary endothelial junctions from oxidate damage that would lead to the leakage of serum proteins."

The Examiner relies on Zikria for the other claimed features, i.e., use of Ringer's lactate solution concentration of the polysaccharide, etc.

GROUPING OF CLAIMS (37 C.F.R. 1.192(c)(5))

As to the rejection applied against claims 1-20 (35 U.S.C. 103), it is the applicant's intention that the rejected claims stand or fall together.

ARGUMENT (37 C.F.R., 1.192(c)(6))

At page 2 of the office action of November 24, 1998, the Examiner notes that the applicant's position, that there is no teaching in the prior art to suggest combining at least one antioxidant with a polysaccharide as specified, in order to prevent leakage of serum proteins from capillary endothelial junctions is, as to the Examiner, not persuasive. He contends that the "person of ordinary skill in the art would have known that oxidative stress on a patient can be overcome by the administration of art recognized antioxidants. Additionally, such oxidative stress would necessarily adversely effect the prevention of leakage of serum proteins from capillary endothelial junctions. When trying to prevent as patient from going into shock, i.e., loss of serum proteins via endothelial capillary junctions, one must obviously reduce all stresses on the persons, that is why the patient is kept warm and an i.v. of hydroxyethyl starch is started. It is simple logic that one should also want to keep the patient protected from oxidative stress by using one or more art recognized antioxidants."

The examiner's "simple logic" solution however has not been reported or resorted to prior to the findings of the applicant in this regard. The antioxidants are given in great extent because of the threat to the integrity of cells from the uncontrolled activity of free radicals. The

Examiner's suggestion that keeping the patient warm as an equivalent is entirely without basis in physiology or medical treatment.

As noted above and in the specification, the prevention of leakage from the capillary endothelial junctions during a period of increased permeability is accomplished by the administration of the hydroxyethyl starch and/or dextran. The antioxidant portion of the composition serves to prevent pathology due to the activity of free radicals.

Zikria teaches a method for preventing leakage of serum albumin from capillary endothelial junctions during a period of increased capillary permeability. That and the method for doing this, i.e., administering certain macromolecules, for example HES, intravenously is all that the Zikria Patent teaches. It does not teach or suggest including an antioxidant for preventing pathology, damage to cells, tissues or organs due to free radical activity.

The Weiss work is directed to determining the effect of superoxide in the destruction of erythrocyte targets by human neutrophils. The destruction mechanism involves O_2 mediated methemoglobin formation with the resultant formation of a cytotoxic peroxide ferrihomo complex. The key to the study was the utilization of the human neutrophil as the source of the oxygen metabolite as this permitted insight into the physiological mechanisms of the target cell destruction and host defense. Superoxide dismutase is one of the materials used. As reported at page 9913 the superoxide dismutase (copper-zinc superoxide dismutase) was used in an experiment to determine the role of O_2 in hemolysis inhibited cytotoxicity. This isolated and very special experimental result is not seen to suggest to the skilled in the art the use of an antioxidant in conjunction with a macromolecule solution as taught by the applicant for the

claimed purpose.

The only suggestion comes from the applicant's specification which is clearly not available. The teaching or suggestion to modify must come from the reference and there is no such teaching here.

Munkes is also a report on the very specific finding and namely that mutants of Neurospora are deficient in certain antioxidants including superoxide dismutase and cAMP and that their survival can be enhanced by "dietary" cAMP or superoxide dismutase. Absolutely nothing in this abstracted experiment suggests combining the macromolecule disclosed by Zikria with the antioxidant disclosed for increasing the survival of mutant Neurospora and that such combination could be administered intravenously for preventing leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effects of free radicals on cellular membranes and organelles.

This teaching is found only in the applicant's disclosure and this cannot be relied on by the Examiner.

Gerdin in the reported abstract discloses that the flavonoid o-(β-hydroxyethyl) rutoside has an inhibitory effect on increased micro vascular permeability induced by various agents in rat skin.

The applicant does not propose that rutoside is effective to inhibit micro vascular permeability (the macromolecule HES or dextran does this) but rather that hydroxyethyl rutoside is effective as an antioxidant to combat pathology due to activity of free radicals.

The Examiner's position that a person of ordinary skill in the art would have known to

combine the antioxidant with hydroxyethyl starch as he has set forth in the office action at page 2 is based on an improper standard of obviousness. The fact that one of ordinary skill in the art has the capabilities to arrive at the invention is not the test whether one of ordinary skill in the art would have arrived at the invention based on the teachings of the prior art. For example, in *Ex parte Levengood,* 28 USPQ 2d 1300 (Bd. Pat. App. & Inter. 1993), all of the patent claims were rejected as obvious in view of the combined teachings of three prior references. The Examiner noted that each reference disclosed a different aspect of the claimed process, and that all these aspects were well known in the art and the modifications to the prior art references were well within the ordinary skill of the art at the time the claimed invention was made.

On appeal, the Board reversed the rejection. As stated by the Board: "At best, the Examiner's comments regarding the obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness . . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness . . . . That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless the logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention."

The *Levengood* decision teaches that the obviousness rejection cannot be predicated on the fact that one of ordinary skill in the art would have the capabilities to arrive at the invention.

This is the situation here and there is reason to believe that "the instant method of modifying the teachings of Zikria, *et al*, by adding one or more of the recognized antioxidants would have been obvious."

CONCLUSION

It is respectfully requested that the Examiner's final rejection be reversed and the claims in the application allowed.

Respectfully submitted.

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APPENDIX

Claims

1. Method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises administering to a subject in need of such treatment an effective amount of a composition comprising at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C, in admixture with a pharmaceutically acceptable liquid carrier.

2. Method according to claim 1 wherein said polysaccharide is hydroxyethyl starch.

3. Method according to claim 1 wherein said polysaccharide is dextran.

4. Method according to claim 1 wherein said polysaccharide is hydroxyethyl starch and dextran.

5. Method according to claim 1 wherein said antioxidant is superoxide dismutase.

6. Method according to claim 1 wherein said antioxidant is catalase.

7. Method according to claim 1 wherein said antioxidant is glutathione peroxidase.

8. Method according to claim 1 wherein said antioxidant is vitamin C.

9. Method according to claim 1 wherein said antioxidant is vitamin C and glutathione peroxidase.

10. Method according to claim 1 wherein said liquid carrier is a member selected from the

group consisting of 0.9% saline, 5% dextrose and Ringer's lactate.

11. Method according to claim 1 wherein said polysaccharide is present in said composition in amount of about 3 to about 50%.

12. Method according to claim 1 wherein said polysaccharide is present in said composition in amount of about 6 to 12%.

13. Method according to claim 1 wherein said composition is administered by intravenous injection in an amount of about 500 to 1500 ml per treatment.

14. Method according to claim 1 wherein said superoxide dismutase is administered in amount of about 5000 to about 20,000 IU/kg per treatment.

15. Method according to claim 6 wherein said catalase is administered in an amount of about 5000 to about 12,500 IU/kg per treatment.

16. Method according to claim 1 wherein said antioxidant is hydroxyethyl rutoside and is administered in an amount of about 500 to about 2000 mg/kg per treatment.

17. Method according to claim 1 wherein said antioxidant is cyclic AMP and is administered in an amount of about 5 to 20 milimols/ml per treatment.

18. Method according to claim 8 wherein said antioxidant is vitamin C and is administered in amount of about 250 to about 2,500 mg/ml per treatment.

19. Method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions during a period of increased capillary permeability and simultaneously preventing the harmful effects of free radicals on cellular membranes and other organelles which comprises intravenously administering to a subject in need of such treatment an effective

amount of a composition comprising:

a) at least one polysaccharide consisting of hydroxyethyl starch and dextran and

b) at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C,

in admixture with a pharmaceutically acceptable liquid carrier selected from the group consisting of 0.9% saline, 5% dextrose and Ringer's lactate and wherein said polysaccharide is present in an amount of about 5 to 12%.

20. A composition for treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C, in admixture with a pharmaceutically acceptable liquid carrier.